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EFFECTS OF DIVIDED DOSES OF X RAY ON MORTALITY AND HEMATOLOGY OF SMALL AND LARGE DOMESTIC ANIMALS

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ADMINISTRATIVE INFORMATION

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ABSTRACT

An attempt to establish a correlation of systemic recovery with hematological recovery after X-radiation exposure for the mouse, rabbit, sheep and goat under uniform experimental conditions is presented. This is part of a continuing program being conducted in this Laboratory in an effort to provide a valid estimate of the rate of recovery in man after radiation exposure by these correlative factors for various species.

By separating these animals into two broad groups, small and large animals, significant differences have been demonstrated as to their LD 50/30, hematological recovery and systemic recovery. Furthermore, a significant departure from the generally accepted exponential recovery after a radiation insult has been shown for both small and large animals. The need for a more critical analysis of recovery at intervals well past the recovery half-time is indicated in evaluating rates of recovery.

SUMMARY

The Problem:

Although there has been an abundance of studies concerned with recovery rates of small animals, there are very few data relating systemic recovery to hematological recovery in large domestic animals. It is our purpose to describe systemic and hematological recovery for both small and large domestic animals.

The Findings:

Data have been presented relating hematological recovery to systemic recovery for the mouse, rabbit, sheep and goat. The small animals (mouse and rabbit) have a higher $LD_{50/30}$ and a relatively short period of hematological and systemic recovery whereas the large animals (sheep and goat) have a lower $LD_{50/30}$ and an extended period of hematological and systemic recovery. The mouse and the rabbit are definitely hypersensitive to doses of radiation at specific time intervals subsequent to an original X-ray exposure. In fact after a radiation insult, there is a significant departure of recovery rates for both small and large animals from the generally accepted exponential recovery concept.

INTRODUCTION

The feasibility of estimating or predicting the recovery rate of man after radiation injury by extrapolating data obtained from recovery studies of experimental animals has long been considered. The usual method of measuring recovery in animals has been the split dose technique (1). It has been generally assumed that after radiation injury, the recovery of animals increases exponentially with time (2,3). Therefore, if a group of animals is first subjected to a single sublethal dose of radiation and then the LD_{50} for these animals determined at various time intervals thereafter, it is possible to calculate the amount of injury remaining or, conversely, the amount of recovery which has occurred after the original radiation exposure. In the present study, recovery half-time or the time required for repair of 50% of the original injury is the index used for comparing recovery in the various species.

Although there has been an abundance of studies concerned with recovery rates of small animals (4,5,6,7,8), there are very little data available concerning the rate of recovery of man after ionizing radiation exposure. The importance of a valid estimate of the rate

of recovery in man after radiation exposure by some correlative factors such as hematological measurements is obvious. Attempts have been made to correlate physiological parameters, such as white blood cell count (9) or basal metabolic rate (10), with recovery half-time for various species. At best, these are merely approximations and are estimates based on data obtained at different laboratories under various conditions. It is our purpose to describe a part of a continuing program being conducted in our Laboratory concerned with a correlation of systemic recovery (recovery half-time) with hematological recovery after X-radiation exposure in eleven animal species under uniform experimental conditions.

METHODS AND MATERIALS

Radiation exposure, dosimetry, and animals

A 1 Mev General Electric X-ray machine was used for all X-radiation exposures (whole body). The target-to-subject distance was 2 meters and the dose rate was 7 r/minute ± 10% (midline air dose). The radiation field was uniform to ± 2-4%. Heavy inherent filtration was used and the HVL was 2.2 g/cm^2 (Pb).

Mice. LaF_1 males, 16 ± 2 weeks of age were placed in lusteroid tubes, X irradiated, and returned to their respective cages.

Rabbits. Male, New Zealand rabbits, 18-24 months old, were housed in individual wire cages and were kept 3-4

weeks prior to X-ray exposure. The animals were irradiated bilaterally in individual lucite boxes.

Sheep. Yearling, castrate Columbia Rambouillet sheep were maintained 3-4 weeks under pasture conditions. The animals were lightly anesthetized with pentabarbital sodium and placed on a rotating canvas holder (1 rpm) to insure a uniform total body X-ray exposure.

Goat. Yearling, castrate, Texas Angora goats were maintained and checked for 3-4 weeks under pasture conditions. Irradiation procedures were identical to those for the sheep.

Experimental design

In order to study recovery by the split dose technique, it was first necessary to determine the LD_{50} for all species used in this program. All LD_{50} values were calculated by standard probit methods (11). Other groups of these species were subjected to a standard 2/3 LD_{50} conditioning dose after which the LD_{50} was redetermined at various time intervals. By redetermining the LD_{50} at these various time intervals, it is possible to calculate a value related to the amount of injury remaining or conversely the amount of recovery occurring after the original conditioning dose.

During the course of these studies, to correlate systemic recovery with hematological recovery, several of the peripheral blood

elements such as granulocytes, mononuclear cells, platelets, and erythrocytes have been critically evaluated as to which might be the best index of hematological recovery. It is our impression to date that the total leucocyte count is as meaningful a determination as any of the others and certainly much easier to obtain. The total leucocyte counts were determined by standard microscopic techniques and also with the Coulter Automatic Cell Counter (12). As a standard measure or index of hematological comparison, we have uniformly accepted the period of one-half maximum depression, i.e., the time interval during which the hematological counts are depressed below one-half the difference between the control and minimal values after radiation exposure.

RESULTS

LD_{50} determination and mean survival time

The $LD_{50/30}$ determinations shown in Table 1 indicate that the relative radiosensitivities of small and large animals differ by at least a factor of 2. The $LD_{50/30}$ range for the small animals is 850-900, whereas the $LD_{50/30}$ range for the large animals is 350-400 r. The widest fiducial limits are seen for the rabbit (843-1009) with an $LD_{50/30}$ of 890 r which is in good agreement with previous studies (13). $LD_{50/30}$ fiducial limits for all other species are essentially within $\pm$ 10%.

Mean survival times for the goat and the sheep are 18 and 21 days, respectively. These times are somewhat longer than those seen for the

TABLE 1

$LD_{50/30}$ Determinations and Mean Survival Time

Species	No. of Animals	$LD_{50/30}$	Fiducial Limits (95%)	Mean Survival Time (days)
Mouse	544	940	(931-950)	12
Rabbit	106	890	(843-1009)	10
Goat	107	412	(368-512)	19
Sheep	67	360	(320-389)	21

mouse and the rabbit. An unusually high percentage of rabbit deaths, approximately 10-20%, occurred during the first two days after X-radiation exposure. This phenomenon is dose independent and has been observed by other investigators.

The LD_{50} data were collected during the 30 days after irradiation for these four species. Goat and sheep survivors were maintained for 60 days and the $LD_{50/60}$ values were not significantly different from the $LD_{50/30}$ values (± 2.5%).

Recovery half-time

In Figure 1, the half-time for recovery of the various species is graphically illustrated. For the mouse, the $LD_{50/30}$ was redetermined at 2, 3, and 4 days, respectively, following the original conditioning exposure. The data indicate that, for the mouse, recovery increases exponentially up to 4-5 days and the recovery half-time is 2.1 days.

The recovery for the rabbit likewise follows an exponential course up to 14 days after a conditioning exposure. However, the rabbit becomes hypersensitive if challenged with a radiation exposure at the 3-week interval as evidenced by an "apparent" increase in percent remaining injury from 40% up to 80%. This "apparent" increase in injury is a transient phenomenon, for by the end of 42 days the rabbit is approximately 80-85% recovered from the 2/3 LD_{50} conditioning dose. Based on the amount of recovery occurring during the first two weeks, the recovery half-time for the rabbit is 9.5 days. Since the animals

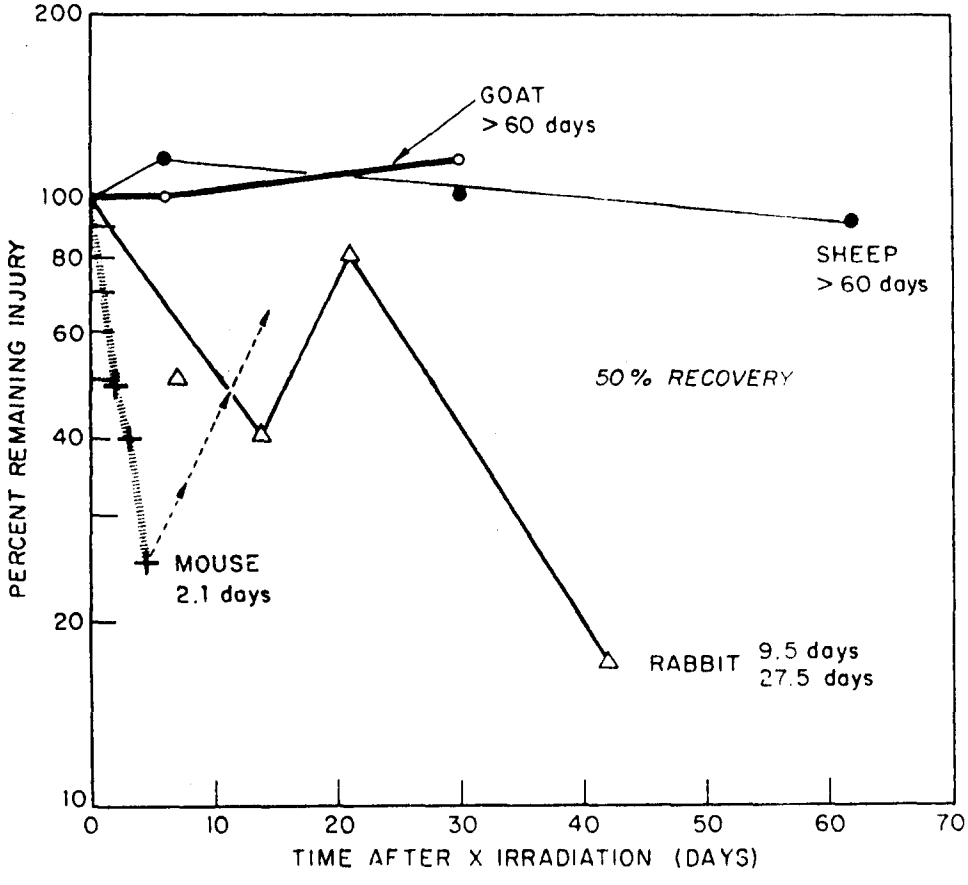

Fig. 1 Recovery half-time of several species after 2/3 LD_{50} X-ray exposure.

reverted to an increased radiosensitive state at the three week period, it is possible to determine another recovery half-time value of 27.5 days. This will be discussed further in another section of this paper.

No significant recovery can be detected in the goat at either 6 or 30 days after the conditioning exposure as shown in Fugure 1. There is a suggestion that the goat, like the rabbit, may be hypersensitive at the 30 day interval although this point has not been clearly established. It is clear, however, that recovery in the goat is a very slow process in comparison to the small animals.

The phenomenon of hypersensitivity or increased radiosensitivity has also been demonstrated for the sheep 6 days after a 2/3 LD_{50} X-radiation exposure. The percent remaining injury at 6 days significantly exceeds 100%. In fact, the redetermined LD_{50} at this time is 40 r $\pm$ 25 which, if added to the 2/3 LD_{50} conditioning exposure, is well below the original $LD_{50/30}$. Again like the goat, the recovery rate for the sheep is exceeding slow as indicated by only 10% recovery at the 60 day period after X-ray exposure.

Hematology

The total leucocyte counts for all species after a 2/3 LD_{50} conditioning exposure are graphically shown as percent of control values in Figure 2. The leucocytes in the mouse decrease rapidly after radiation exposure to minimum values within 5 days with indications of leucocyte recovery taking place by approximately 10 days. The duration

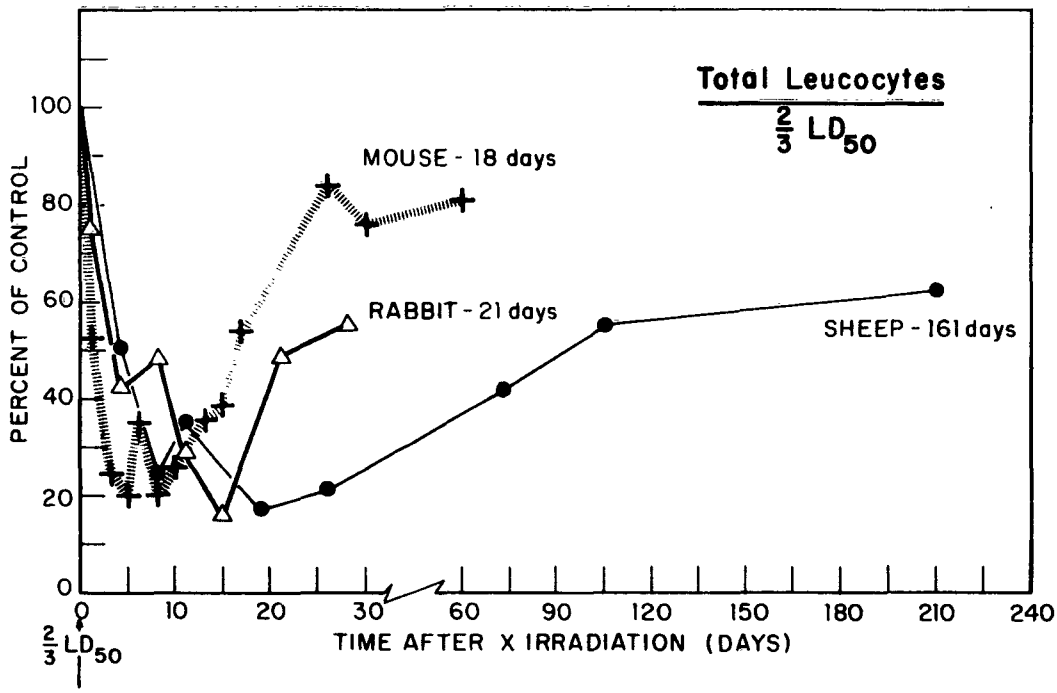

Fig. 2 Recovery patterns of total leucocytes after 2/3 LD_{50} X-ray exposure.

of one-half maximum depression which is our standard value for comparisons between species is 18 days for the mouse.

The decrease in leucocytes for the rabbit is not quite as rapid as for the mouse, reaching a minimum at 12-15 days in the former case. Recovery processes apparently begin shortly thereafter with leucocyte values reaching 80% of control within 30 days. The duration of one-half maximum depression for the rabbit is 21 days.

In sheep, minimum values of leucocytes are not reached until 16-20 days with an apparent increase taking place within 30 days. However, complete recovery of the leucocytes is not attained even at 265 days post-irradiation. The duration of one-half maximum depression for the sheep is 161 days.

Hematological responses for the goat are in the preliminary stage and will not be presented at this time. However, the available data suggest that the hematological recovery in the goat is significantly slower than in small animals.

A correlation of hematological recovery with systemic recovery (half-time) is shown in Table 2 for all four species. There is a significant difference between large and small animals. In comparing recovery, both hematologically and systemically, the large animals differ temporally from the small animals by a factor approximating 2.

DISCUSSION

Although previous reports by Davidson (9) and Michaelson (10)

TABLE 2

Hematological and Systemic Recovery

Species	Duration of 1/2 Maximum Depression of Leucocytes (days)	Half-time of Systemic Recovery (days)
Mouse	18	2.1
Rabbit	21	9.5, 27.5
Goat	> 40 *	> 60
Sheep	161	> 60

* Experiments still in progress

have indicated a consistent pattern of species response and recovery with relation to recovery half-time after radiation exposure, we have not been able to observe any specific pattern of "ordering of species" in the $LD_{50/30}$ determinations. It is possible only to classify the $LD_{50/30}$ for all species into two broad groups; the small animals such as the rodents and rabbits which have a high $LD_{50/30}$, 800-900 rad, and the large animals such as the sheep, goat, swine (14), and burro (14) which have a low $LD_{50/30}$, 350-450 rad. This separation of a broad spectrum of species into large animals - low $LD_{50/30}$ and small animals - high $LD_{50/30}$ lends credence to the hypothesis that man may fall into the category of large animals insofar as recovery half-time is concerned. Thus, it is highly possible that a valid estimate or prediction of the rate of recovery can be made for men after radiation injury by measuring some physiological variables.

The hematological response of the various animals determined in our laboratory supports, in general, the assumption of Davidson only insofar as there is a difference in recovery rates between large and small animals. The leucocyte counts show that the initial decrease to minimum values occurs sooner for the small animals and the subsequent increase in leucocyte values occurs sooner. The duration of one-half maximum depression, our index of hematological recovery, is approximately 18-20 days and 40-161 days for small and large animals, respectively.

There has been a great deal of discussion concerning the dependence of repair half-time on the size of the original conditioning dose (4,15,16,17). However, this factor does not enter into our experiments since we employ a standard original conditioning dose, 2/3 LD_{50}. A more important question is whether the repair process is exponential with time as is generally assumed, and whether there is any correlation with hematological recovery. It is quite interesting to note that with conditioning doses of 2/3 LD_{50}, the recovery of some animals in this report follows an exponential course with time well past the 50% recovery half-time interval. This is particularly true in the case of small animals such as rats (14), mice, hamsters (14), and rabbits where recovery is quite rapid. Recovery in the rabbit increases exponentially with time and approaches values of 60% recovery within two weeks after the initial radiation insult. However, the finding that these animals are radiosensitive at the three-week period suggests that some critical organ system has undergone some alteration such that little additional radiation is required to kill the animal. It is not possible to describe the specific system or systems involved in this phenomenon of altered radiosensitivity at this time. There is no indication that this change in radiosensitivity is reflected in the changes of the peripheral blood elements. At the 3-week time period when the increased radiosensitivity is observed in the rabbit, the total leucocyte count is well on the way to recovery. Therefore, there is no correlation of hematological changes with this hypersensitive state.

Similar observations of altered radiosensitivity to subsequent X-radiation after a conditioning exposure have been observed for the mouse. Recent experiments in our Laboratory have shown that mice previously exposed to neutron radiation (2/3 LD_{50}) and then subsequently challenged 5 and 15 days later are recovered in excess of 75% at the 5 day interval but become hypersensitive at the 15 day interval. This alteration of radiosensitivity is indicated for the mouse by the dotted line and arrows as shown in Figure 1. This demonstration of an alteration in radiosensitivity at various time intervals after a conditioning X-ray exposure in several species introduces a new problem in radiobiology. Furthermore, a critical analysis of recovery at intervals past the recovery half-time is essential in evaluating rates of recovery and the true significance of these values.

SUMMARY

Data have been presented relating hematological recovery to systemic recovery for the mouse, rabbit, sheep, and goat. By separating these animals into two broad groups, small and large animals, significant differences have been demonstrated as to their $LD_{50/30}$, hematological recovery and systemic recovery. The small animals have a higher $LD_{50/30}$ and a relatively short period of hematological and systemic recovery whereas the large animals have a lower $LD_{50/30}$ and an extended period of hematological and systemic recovery. A significant departure from the generally accepted exponential increase in recovery after a radiation insult has been demonstrated for both small and large animals.

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